Neuroscientist 2018 vol.24 N2, pages 130-141

Ethanol and the Developing Brain: Inhibition of Neuronal Activity and Neuroapoptosis

Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia

Abstract

© 2017, © The Author(s) 2017. Ethanol induces massive neuroapoptosis in the developing brain. One of the main hypotheses that has been put forward to explain the deleterious actions of ethanol in the immature brain involves an inhibition of neuronal activity. Here, we review recent evidence for this hypothesis obtained in the somatosensory cortex and hippocampus of neonatal rodents. In both structures, ethanol strongly inhibits brain activity. At the doses inducing massive neuroapoptosis, ethanol completely suppresses the early activity patterns of spindle-bursts and gamma oscillations in the neocortex and the early sharp-waves in the hippocampus. The inhibitory effects of ethanol decrease with age and in adult animals, ethanol only mildly depresses neuronal firing and induces delta-wave activity. Suppression of cortical activity in neonatal animals likely involves inhibition of the myoclonic twitches, an important physiological trigger for the early activity bursts, and inhibition of the thalamocortical and intracortical circuits through a potentiation of GABAergic transmission and an inhibition of N-methyl-d-aspartate (NMDA) receptors, that is in keeping with the neuroapoptotic effects of other agents acting on GABA and NMDA receptors. These findings provide support for the hypothesis that the ethanol-induced inhibition of cortical activity is an important pathophysiological mechanism underlying massive neuroapoptosis induced by ethanol in the developing brain.

http://dx.doi.org/10.1177/1073858417712667

Keywords

apoptosis, electroencephalogram, ethanol, fetal alcohol syndrome, GABA, NMDA

References

[1] Akhmetshina D, Nasretdinov A, Zakharov A, Valeeva G, Khazipov R., 2016. The nature of the sensory input to the neonatal rat barrel cortex. J Neurosci 36(38):9922–32.

[2] Allene C, Cattani A, Ackman JB, Bonifazi P, Aniksztejn L, Ben-Ari Y, and others. 2008. Sequential generation of two distinct synapse-driven network patterns in developing neocortex. J Neurosci 28(48):12851–63.

[3] Bauer-Moffett C, Altman J., 1977. The effect of ethanol chronically administered to preweanling rats on cerebellar development: a morphological study. Brain Res 119(2):249–68.

[4] Ben-Ari Y, Cherubini E, Corradetti R, Gaiarsa J-L., 1989. Giant synaptic potentials in immature rat CA3 hippocampal neurones. J Physiol 416:303–25.

[5] Bittigau P, Sifringer M, Genz K, Reith E, Pospischil D, Govindarajalu S, and others. 2002. Antiepileptic drugs and apoptotic neurodegeneration in the developing brain. Proc Natl Acad Sci U S A 99(23):15089–94.

[6] Blankenship AG, Feller MB. 2010. Mechanisms underlying spontaneous patterned activity in developing neural circuits. Nat Rev Neurosci 11(1):18–29.

[7] Bolea S, Avignone E, Berretta N, Sanchez-Andres JV, Cherubini E., 1999. Glutamate controls the induction of GABA-mediated giant depolarizing potentials through AMPA receptors in neonatal rat hippocampal slices. J Neurophysiol 81(5):2095–102.

[8] Chernova K, Burkhanova G, Zakharov A, Khazipov R, Sitdikova G., 2017. Inhibitory effects of ethanol in the neonatal rat hippocampus in vivo. BioNanoScience 7:159.

[9] Colonnese MT, Khazipov R., 2010. “Slow activity transients” in infant rat visual cortex: a spreading synchronous oscillation patterned by retinal waves. J Neurosci 30(12):4325–37.

[10] Colonnese M, Khazipov R., 2012. Spontaneous activity in developing sensory circuits: Implications for resting state fMRI. Neuroimage 62(4):2212–21.

[11] Creeley CE, Olney JW. 2013. Drug-induced apoptosis: mechanism by which alcohol and many other drugs can disrupt brain development. Brain Sci 3(3):1153–81.

[12] Daw MI, Ashby MC, Isaac JT. 2007. Coordinated developmental recruitment of latent fast spiking interneurons in layer IV barrel cortex. Nat Neurosci 10(4):453–61.

[13] Dikranian K, Qin YQ, Labruyere J, Nemmers B, Olney JW. 2005. Ethanol-induced neuroapoptosis in the developing rodent cerebellum and related brain stem structures. Dev Brain Res 155(1):1–13.

[14] Dildymayfield JE, Harris RA. 1995. Ethanol inhibits kainate responses of glutamate receptors expressed in xenopus oocytes—role of calcium and protein-kinase-C. J Neurosci 15(4):3162–71.

[15] Dunty WC, Jr Chen SY, Zucker RM, Dehart DB, Sulik KK. 2001. Selective vulnerability of embryonic cell populations to ethanol-induced apoptosis: implications for alcohol-related birth defects and neurodevelopmental disorder. Alcohol Clin Exp Res 25(10):1523–35.

[16] Dupont E, Hanganu IL, Kilb W, Hirsch S, Luhmann HJ. 2006. Rapid developmental switch in the mechanisms driving early cortical columnar networks. Nature 439(7072):79–83.

[17] Dzhala VI, Talos DM, Sdrulla DA, Brumback AC, Mathews GC, Benke TA, and others. 2005. NKCC1 transporter facilitates seizures in the developing brain. Nat Med 11(11):1205–13.

[18] Farber NB, Olney JW. 2003. Drugs of abuse that cause developing neurons to commit suicide. Dev Brain Res 147(1–2):37–45.

[19] Galindo R, Zamudio PA, Valenzuela CF. 2005. Alcohol is a potent stimulant of immature neuronal networks: implications for fetal alcohol spectrum disorder. J Neurochem 94(6):1500–11.

[20] Girault V, Gilard V, Marguet F, Lesueur C, Hauchecorne M, Ramdani Y, and others. 2017. Prenatal alcohol exposure impairs autophagy in neonatal brain cortical microvessels. Cell Death Dis 8(2):e2610.

[21] Golbs A, Nimmervoll B, Sun JJ, Sava IE, Luhmann HJ. 2011. Control of programmed cell death by distinct electrical activity patterns. Cereb Cortex 21(5):1192–202.

[22] Golshani P, Jones EG. 1999. Synchronized paroxysmal activity in the developing thalamocortical network mediated by corticothalamic projections and “silent” synapses. J Neurosci 19(8):2865–75.

[23] Hagenston AM, Bading H., 2011. Calcium signaling in synapse-to-nucleus communication. Cold Spring Harb Perspect Biol 3(11):a004564.

[24] Hanganu IL, Ben Ari Y, Khazipov R., 2006. Retinal waves trigger spindle bursts in the neonatal rat visual cortex. J Neurosci 26(25):6728–36.

[25] Hanganu-Opatz IL, 2010. Between molecules and experience: role of early patterns of coordinated activity for the development of cortical maps and sensory abilities. Brain Res Rev 64(1):160–76.

[26] Harris RA., 1999. Ethanol actions on multiple ion channels: which are important? Alcohol Clin Exp Res 23(10):1563–70.

[27] Heck N, Golbs A, Riedemann T, Sun JJ, Lessmann V, Luhmann HJ. 2008. Activity-dependent regulation of neuronal apoptosis in neonatal mouse cerebral cortex. Cereb Cortex. 18(6):1335–49.

[28] Hwang JY, Kim YH, Ahn YH, Wie MB, Koh JY. 1999. N-methyl-d-aspartate receptor blockade induces neuronal apoptosis in cortical culture. Exp Neurol 159(1):124–30.

[29] Ikonomidou C. 2009. Triggers of apoptosis in the immature brain. Brain Dev. 31(7):488–92.

[30] Ikonomidou C, Bittigau P, Ishimaru MJ, Wozniak DF, Koch C, Genz K, and others. 2000. Ethanol-induced apoptotic neurodegeneration and fetal alcohol syndrome. Science 287(5455):1056–60.

[31] Ikonomidou C, Bosch F, Miksa M, Bittigau P, Vöckler J, Dikranian K, and others. 1999. Blockade of NMDA receptors and apoptotic neurodegeneration in the developing brain. Science 283(5398):70–4.

[32] Inacio AR, Nasretdinov A, Lebedeva J, Khazipov R., 2016. Sensory feedback synchronizes motor and sensory neuronal networks in the neonatal rat spinal cord. Nat Commun 7:13060.

[33] Jevtovic-Todorovic V, Hartman RE, Izumi Y, Benshoff ND, Dikranian K, Zorumski CF, and others. 2003. Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. J Neurosci 23(3):876–82.

[34] Jégou S, El Ghazi F, de Lendeu PK, Marret S, Laudenbach V, Uguen A, and others. 2012. Prenatal alcohol exposure affects vasculature development in the neonatal brain. Ann Neurol 72(6):952–60.

[35] Karlsson KA, Mohns EJ, di Prisco GV, Blumberg MS. 2006. On the co-occurrence of startles and hippocampal sharp waves in newborn rats. Hippocampus. 16(11):959–65.

[36] Khalilov I, Dzhala V, Ben-Ari Y, Khazipov R., 1999. Dual role of GABA in the neonatal rat hippocampus. Dev Neurosci. 21(3–5):310–9.

[37] Khalilov I, Minlebaev M, Mukhtarov M, Khazipov R., 2015. Dynamic changes from depolarizing to hyperpolarizing GABAergic actions during giant depolarizing potentials in the neonatal rat hippocampus. J Neurosci 35(37):12635–42.

[38] Khazipov R, Luhmann HJ. 2006. Early patterns of electrical activity in the developing cerebral cortex of humans and rodents. Trends Neurosci 29(7):414–8.

[39] Khazipov R, Minlebaev M, Valeeva G., 2013. Early gamma oscillations. Neuroscience 250:240–52.

[40] Khazipov R, Sirota A, Leinekugel X, Holmes GL, Ben Ari Y, Buzsaki G., 2004. Early motor activity drives spindle bursts in the developing somatosensory cortex. Nature 432(7018):758–61.

[41] Kidd FL, Isaac JT. 1999. Developmental and activity-dependent regulation of kainate receptors at thalamocortical synapses. Nature 400(6744):569–73.

[42] Kilb W, Kirischuk S, Luhmann HJ. 2011. Electrical activity patterns and the functional maturation of the neocortex. Eur J Neurosci 34(10):1677–86.

[43] Kilb W, Kirischuk S, Luhmann HJ. 2013. Role of tonic GABAergic currents during pre- and early postnatal rodent development. Front Neural Circuits 7:139.

[44] Kirmse K, Kummer M, Kovalchuk Y, Witte OW, Garaschuk O, Holthoff K., 2015. GABA depolarizes immature neurons and inhibits network activity in the neonatal neocortex in vivo. Nat Commun 6:7750.

[45] Lamsa K, Palva JM, Ruusuvuori E, Kaila K, Taira T., 2000. Synaptic GABA(A) activation inhibits AMPA-kainate receptor-mediated bursting in the newborn (P0-P2) rat hippocampus. J Neurophysiol 83(1):359–66.

[46] Lebedeva J, Zakharov A, Ogievetsky E, Minlebaeva A, Kurbanov R, Gerasimova E, and others. 2017. Inhibition of cortical activity and apoptosis caused by ethanol in neonatal rats in vivo. Cereb Cortex 27(2):1068–82.

[47] Lebedeva YA, Zakharova AV, Sitdikova GF, Zefirov AL, Khazipov RN. 2016. Ketamine-midazolam anesthesia induces total inhibition of cortical activity in the brain of newborn rats. Bull Exp Biol Med 161(1):15–19.

[48] Leinekugel X, Khazipov R, Cannon R, Hirase H, Ben Ari Y, Buzsaki G., 2002. Correlated bursts of activity in the neonatal hippocampus in vivo. Science 296(5575):2049–52.

[49] Leveille F, Papadia S, Fricker M, Bell KF, Soriano FX, Martel MA, and others. 2010. Suppression of the intrinsic apoptosis pathway by synaptic activity. J Neurosci 30(7):2623–35.

[50] Lovinger DM, White G, Weight FF. 1989. Ethanol inhibits NMDA-activated ion current in hippocampal neurons. Science 243(4899):1721–4.

[51] Luhmann HJ, Sinning A, Yang JW, Reyes-Puerta V, Stuttgen MC, Kirischuk S, and others. 2016. Spontaneous neuronal activity in developing neocortical networks: from single cells to large-scale interactions. Front Neural Circuits. 10:40.

[52] Luo J. 2012. Mechanisms of ethanol-induced death of cerebellar granule cells. Cerebellum. 11(1):145–54.

[53] Masood K, Wu CP, Brauneis U, Weight FF. 1994. Differential ethanol sensitivity of recombinant N-methyl-d-aspartate receptor subunits. Mol Pharmacol 45(2):324–9.

[54] Mattson SN, Crocker N, Nguyen TT. 2011. Fetal alcohol spectrum disorders: neuropsychological and behavioral features. Neuropsychol Rev 21(2):81–101.

[55] Mennerick S, Zorumski CF. 2000. Neural activity and survival in the developing nervous system. Mol Neurobiol. 22(1–3):41–54.

[56] Minlebaev M, Ben-Ari Y, Khazipov R., 2009. NMDA receptors pattern early activity in the developing barrel cortex in vivo. Cereb Cortex. 19(3):688–96.

[57] Minlebaev M, Ben-Ari Y, Khazipov R., 2007. Network mechanisms of spindle-burst oscillations in the neonatal rat barrel cortex in vivo. J Neurophysiol 97(1):692–700.

[58] Minlebaev M, Colonnese M, Tsintsadze T, Sirota A, Khazipov R., 2011. Early gamma oscillations synchronize developing thalamus and cortex. Science 334(6053):226–9.

[59] Mody I, Glykys J, Wei WZ. 2007. A new meaning for “gin & tonic”: tonic inhibition as the target for ethanol action in the brain. Alcohol 41(3):145–53.

[60] Mohns EJ, Blumberg MS. 2010. Neocortical activation of the hippocampus during sleep in infant rats. J Neurosci 30(9):3438–49.

[61] Monyer H, Burnashev N, Laurie DJ, Sakmann B, Seeburg PH. 1994. Developmental and regional expression in the rat brain and functional properties of four NMDA receptors. Neuron 12(3):529–40.

[62] Morton RA, Valenzuela CF. 2016. Further characterization of the effect of ethanol on voltage-gated Ca channel function in developing CA3 hippocampal pyramidal neurons. Brain Res 1633:19–26.

[63] Nikolic M, Gardner HA, Tucker KL. 2013. Postnatal neuronal apoptosis in the cerebral cortex: physiological and pathophysiological mechanisms. Neuroscience 254:369–78.

[64] Nimmervoll B, White R, Yang JW, An SM, Henn C, Sun JJ, and others. 2013. LPS-induced microglial secretion of TNF alpha increases activity-dependent neuronal apoptosis in the neonatal cerebral cortex. Cereb Cortex 23(7):1742–55.

[65] Ogievetsky E, Lotfullina N, Minlebaeva A, Khazipov R., 2016. Ethanol-induced apoptosis of interneurons in the neonatal GAD67-GFP mouse hippocampus. BioNanoScience. Epub Oct. doi:10.1007/s12668-016-0334-6.

[66] Olney JW, Tenkova T, Dikranian K, Muglia LJ, Jermakowicz WJ, D'Sa C, and others. 2002a. Ethanol-induced caspase-3 activation in the in vivo developing mouse brain. Neurobiol Dis 9(2):205–19.

[67] Olney JW, Tenkova T, Dikranian K, Qin YQ, Labruyere J, Ikonomidou C., 2002b. Ethanol-induced apoptotic neurodegeneration in the developing C57BL/6 mouse brain. Dev Brain Res 133(2):115–26.

[68] Olney JW, Young C, Wozniak DF, Jevtovic-Todorovic V, Ikonomidou C., 2004. Do pediatric drugs cause developing neurons to commit suicide? Trends Pharmacol Sci 25(3):135–9.

[69] Olney JW. 2014. Focus on apoptosis to decipher how alcohol and many other drugs disrupt brain development. Front Pediatr 2:81.

[70] Sitdikova G, Zakharov A, Janackova S, Gerasimova E, Lebedeva J, Inacio AR, and others. 2014. Isoflurane suppresses early cortical activity. Ann Clin Transl Neurol. 1(1):15–26.

[71] Stobbs SH, Ohran AJ, Lassen MB, Allison DW, Brown JE, Steffensen SC. 2004. Ethanol suppression of ventral tegmental area GABA neuron electrical transmission involves N-methyl-d-aspartate receptors. J Pharmacol Exp Ther 311(1):282–9.

[72] Tenkova T, Young C, Dikranian K, Labruyere J, Olney JW. 2003. Ethanol-induced apoptosis in the developing visual system during synaptogenesis. Invest Ophthalmol Vis Sci 44(7):2809–17.

[73] Tiriac A, Uitermarkt BD, Fanning AS, Sokoloff G, Blumberg MS. 2012. Rapid whisker movements in sleeping newborn rats. Curr Biol 22(21):2075–80.

[74] Turner CP, DeBenedetto D, Liu C., 2009. NMDAR blockade-induced neonatal brain injury: reversal by the calcium channel agonist BayK 8644. Neurosci Lett 450(3):292–5.

[75] Valeeva G, Abdullin A, Tyzio R, Skorinkin A, Nikolski E, Ben-Ari Y, and others. 2010. Temporal coding at the immature depolarizing GABAergic synapse. Front Cell Neurosci 4.

[76] Valeeva G, Tressard T, Mukhtarov M, Baude A, Khazipov R., 2016. An optogenetic approach for investigation of excitatory and inhibitory network GABA actions in mice expressing channelrhodopsin-2 in GABAergic neurons. J Neurosci 36(22):5961–73.

[77] Wells JE, Porter JT, Agmon A., 2000. GABAergic inhibition suppresses paroxysmal network activity in the neonatal rodent hippocampus and neocortex. J Neurosci 20(23):8822–30.

[78] West JR, Hamre KM, Cassell MD. 1986. Effects of ethanol exposure during the third trimester equivalent on neuron number in rat hippocampus and dentate gyrus. Alcohol Clin Exp Res 10(2):190–7.

[79] Wright JM, Peoples RW, Weight FF. 1996. Single-channel and whole-cell analysis of ethanol inhibition of NMDA-activated currents in cultured mouse cortical and hippocampal neurons. Brain Res. 738(2):249–56.

[80] Xu W, Cormier R, Fu T, Covey DF, Isenberg KE, Zorumski CF, and others. 2000. Slow death of postnatal hippocampal neurons by GABA receptor overactivation. J Neurosci 20(9):3147–56.

[81] Yang JW, An S, Sun JJ, Reyes-Puerta V, Kindler J, Berger T, and others. 2013. Thalamic network oscillations synchronize ontogenetic columns in the newborn rat barrel cortex. Cereb Cortex 23(6):1299–316.

[82] Yang JW, Hanganu-Opatz IL, Sun JJ, Luhmann HJ. 2009. Three patterns of oscillatory activity differentially synchronize developing neocortical networks in vivo. J Neurosci 29(28):9011–25.

[83] Young C, Klocke BJ, Tenkova T, Choi J, Labruyere J, Qin YQ, and others. 2003. Ethanol-induced neuronal apoptosis in vivo requires BAX in the developing mouse brain. Cell Death Differ 10(10):1148–55.

[84] Young C, Roth KA, Klocke BJ, West T, Holtzman DM, Labruyere J, and others. 2005. Role of caspase-3 in ethanol-induced developmental neurodegeneration. Neurobiol Dis 20(2):608–14.

[85] Young CL, Straiko MM, Johnson SA, Creeley C, Olney JW. 2008. Ethanol causes and lithium prevents neuroapoptosis and suppression of pERK in the infant mouse brain. Neurobiol Dis 31(3):355–60.

[86] Zhong J, Yang XL, Yao WG, Lee WH. 2006. Lithium protects ethanol-induced neuronal apoptosis. Biochem Biophys Res Commun 350(4):905–10.